in Fig. 5A as issued as well as in the original Fig. 5A as filed.

'554 Patent - Fig. 5A *As Issued*

- Three main errors that need correction:
  - LE is incorrect (should be VQ)
  - F in box is incorrect (should be outside)
  - codon for I (ATT) should be ATC

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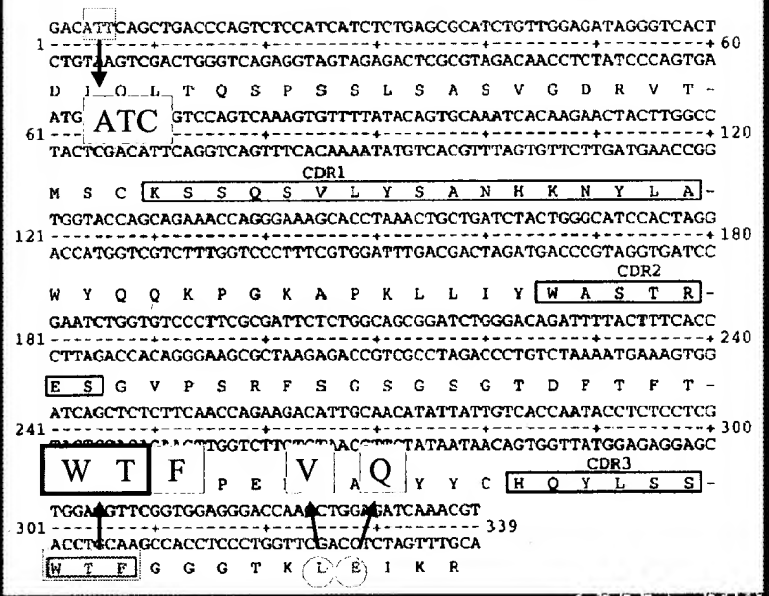
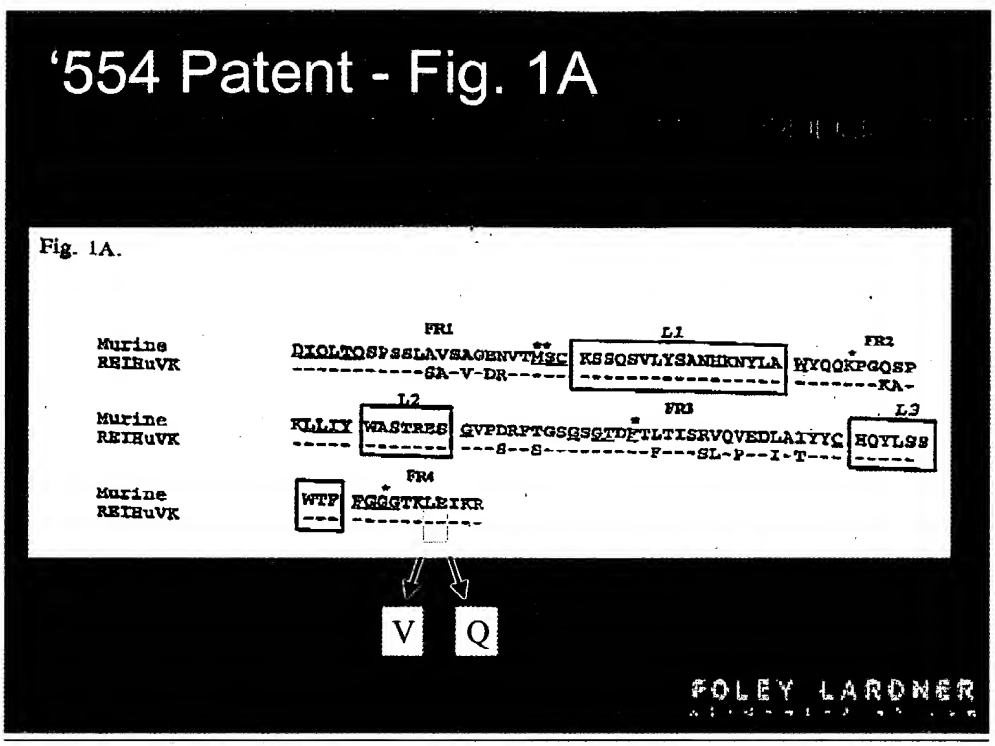
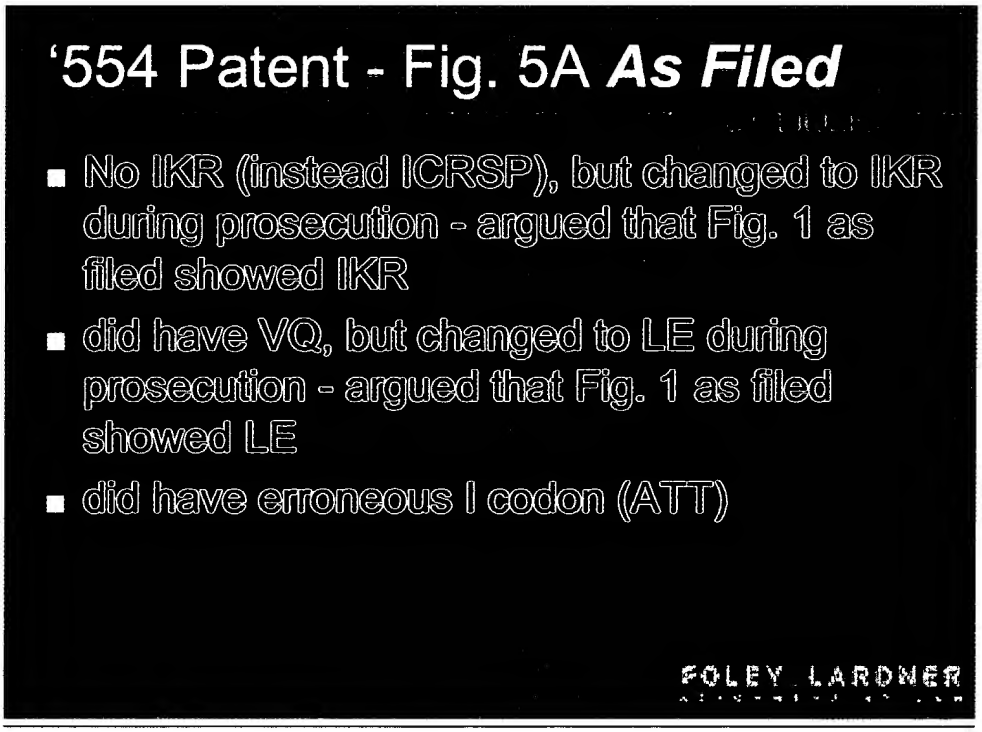
FIG. 5A

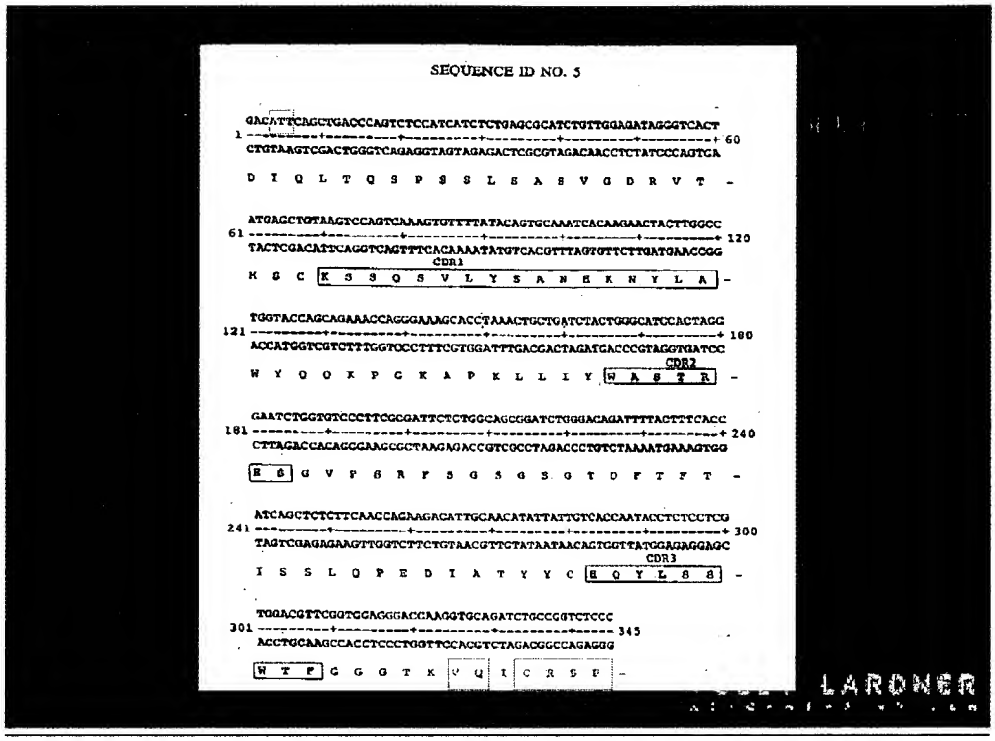


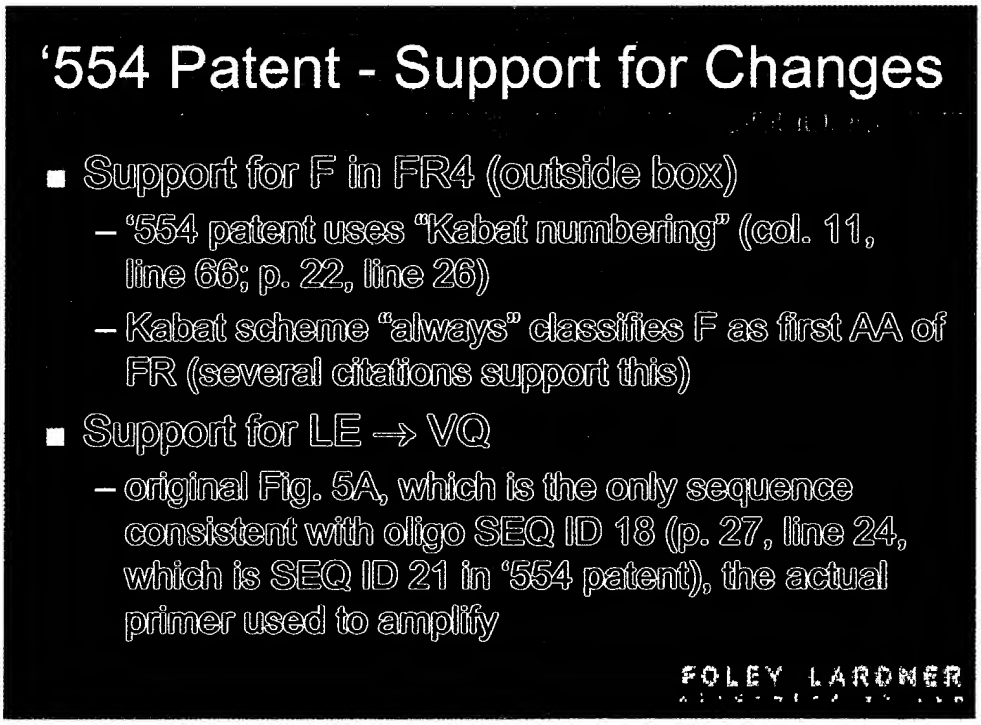




As summarized in the slide immediately above, arguments were made for certain sequence changes based on Fig. 1 during prosecution of the parent patent. The change to IKR was correct, but the change of VQ to LE was incorrect (at the time these arguments were made in the parent patent, LE was thought to be correct). As shown below, however, there are several reasons why one of ordinary skill in the art would have realized that VQ should not have been changed and that IKR was a correct change. In addition, as discussed

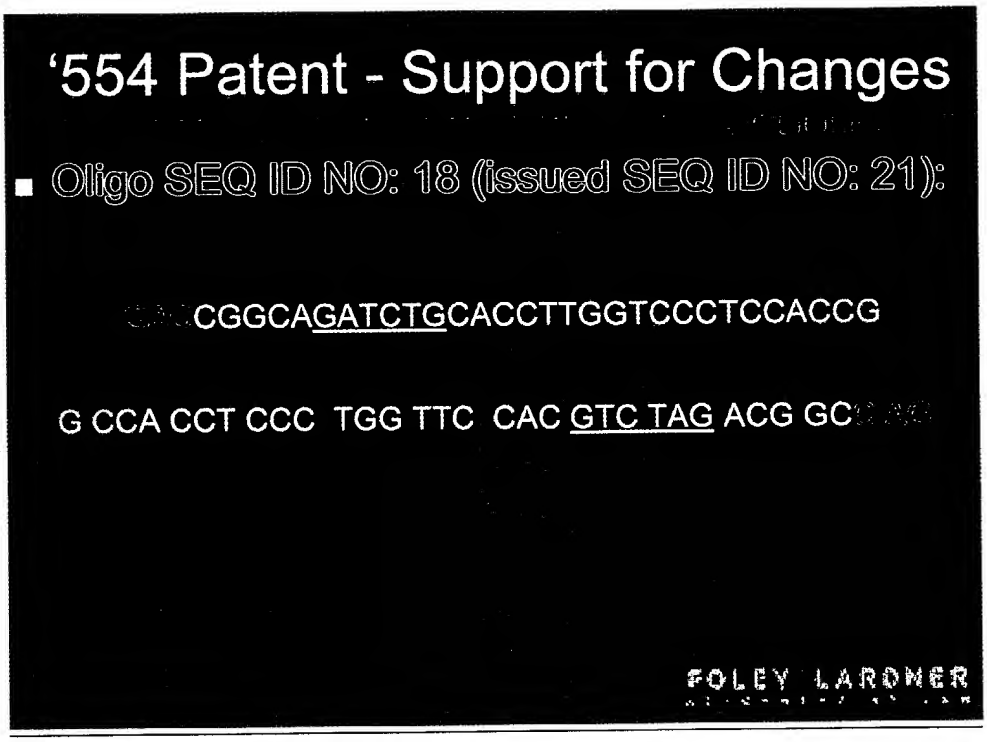
at the interview, applicants have made a deposit of the material containing the correct sequence which further supports the changes being made.

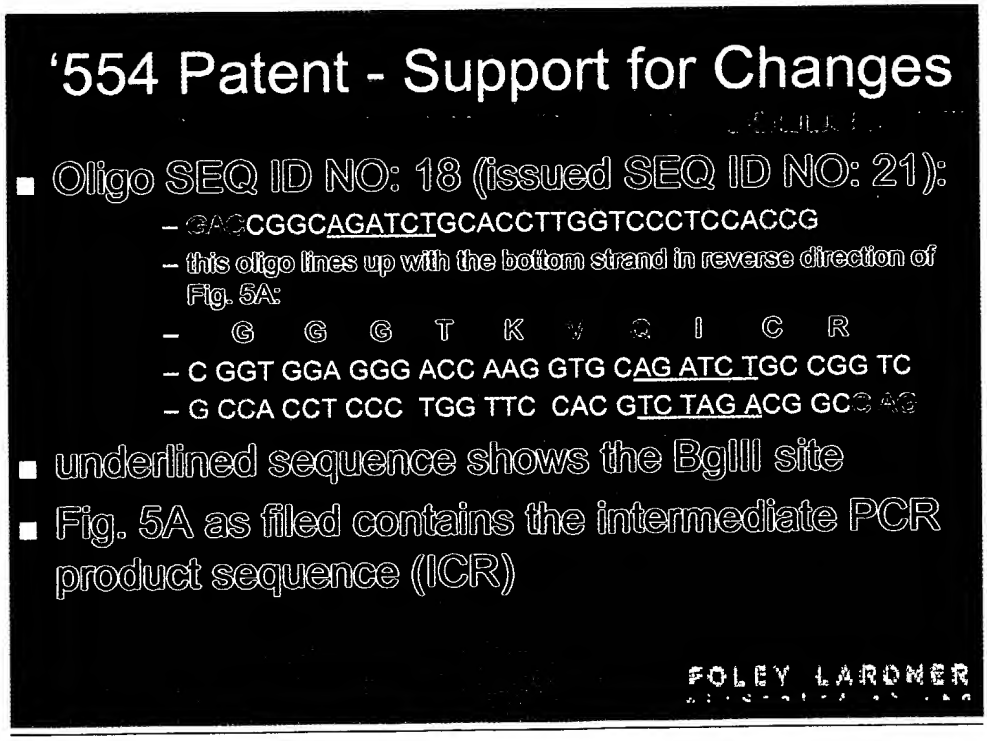




The corresponding reference to the "Kabat numbering" is found on page 22, lines 4-13 and lines 25-29 of the specification. Applicants will provide a copy of Kabat shortly under separate cover that discloses that the first amino acid residue of the FR4 is always

"F." Additionally as noted above, original Fig. 5A contained the "VQ" in FR4 "FGGGTKVQICRSP." These two amino acid sequences were incorrectly changed to the corresponding murine sequences during prosecution of the '554 patent. As noted above, SEQ ID NO:21 (SEQ ID NO:18 as originally filed) supports this sequence.





'554 Patent - Support for Changes

- Support for IKR & further support for VQ
- BclI site used in staging vector (col. 15, lines 21-26; p. 28, lines 1-6) introduces the first A of K codon & BglII requires A of Q codon:
  - the previous BglII cut is depicted as follows:
    - Q I C R S P
    - CAGATC TGC CGG TCT CCC
  - the product to the left of the red line above is then ligated into the BclI site of the staging vector:
    - Q I K R
    - CAGATC AAA CGT

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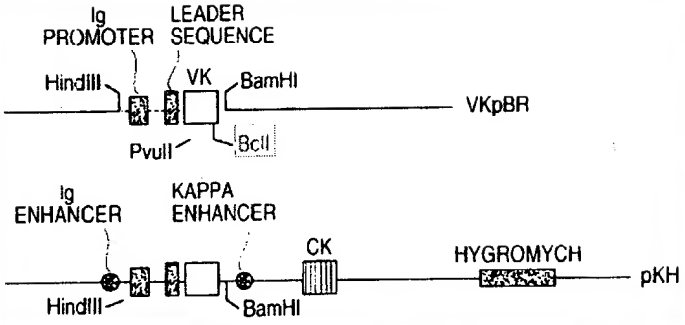
'554 Patent - Support for Changes

FIG. 3A



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'554 Patent - Support for Changes

- a C (as shown in original Fig. 5A) would be incompatible with use of BclI (codon must start with a T), but a K (as shown in original Fig. 1A) is compatible (codon starts with A)
- one of ordinary skill in the art would resolve the conflict between IKR (original Fig. 1A) and ICRSP (original Fig. 5A) based on the restriction sites & oligo SEQ ID 18 in favor of IKR
- this is not inconsistent with choosing VQ from Fig. 5A because that choice is also dictated by the restriction sites which require Q and oligo SEQ ID 18
- BglII/BclI sites are consistent with the sequence of oligo SEQ ID 18 (issued SEQ ID 21) - anchor for all changes

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'554 Patent - Support for Changes

- Further support comes from Orlandi
- intron removal in expression vector creates final IKR subsequence
  - "The VK and VH sequences for cLL2 or hLL2 can [be] amplified by PCR as described in Orlandi et al. (*Proc. Natl. Acad. Sci., USA*, 86:3833 (1989)) which is incorporated by reference" (col. 8, lines 1-4; p. 15, lines 3-6)
  - Orlandi at p. 3834, right column, lines 6-9, and in Fig. 2 legend cites to Riechmann (*Nature*, 332(1988): 323-327), for explanation of non-coding regions
  - Riechmann (p. 324, legend of Fig. 1), in turn, cites to Hieter (*Cell*, 22(1980): 197-201) for an explanation of "the 3' non-coding sequence taken from a human J_K-region sequence"

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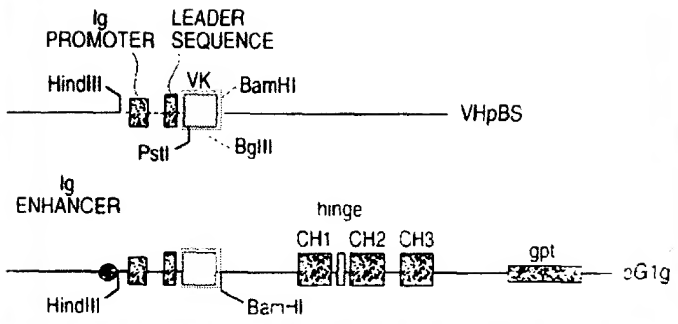
'554 Patent - Fig. 3B

FIG. 3B



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'554 Patent - Support for Changes

- HindIII/BamHI fragment was subcloned into the expression vector, pKh, where it was linked to the genomic DNA for Ck, including introns and exon:
- ... ... AAACgt... ...ggatcc... ...agGAAGTGTG... ...
- ... ... K T V ... ...
- UPPERCASE, exon; lowercase, intron; Underlined, BamHI site; bold, splicing donor and acceptor
- Blue shows the sequence from VKpBR and red shows that from pKh. Note that the coding sequences for Vk and Ck are discontinued. The stop codon is at the end of Ck sequence.

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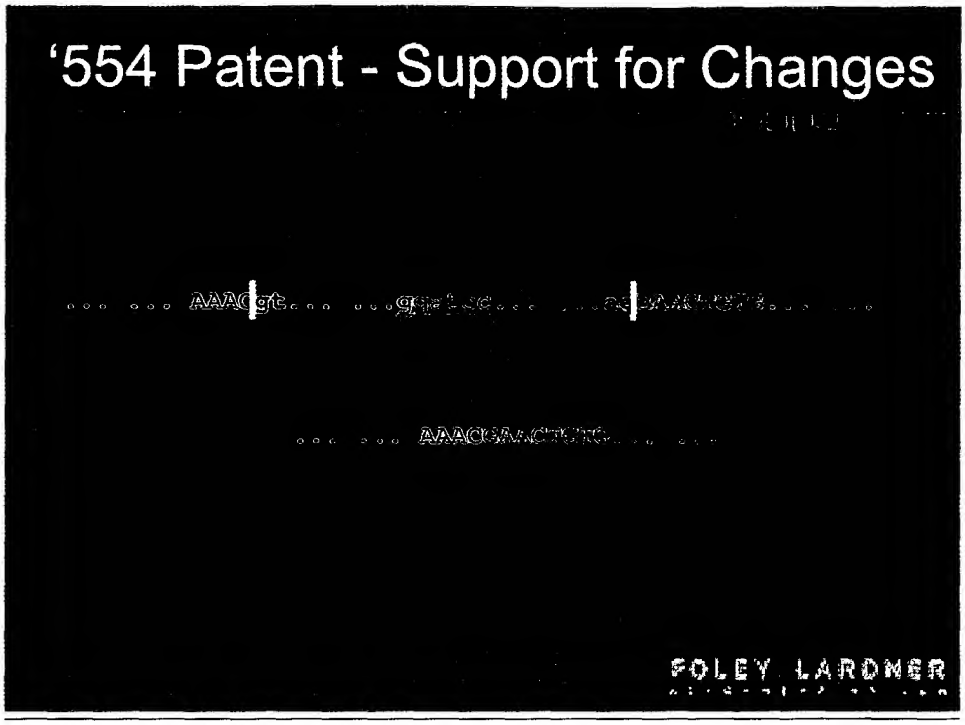
'554 Patent - Support for Changes
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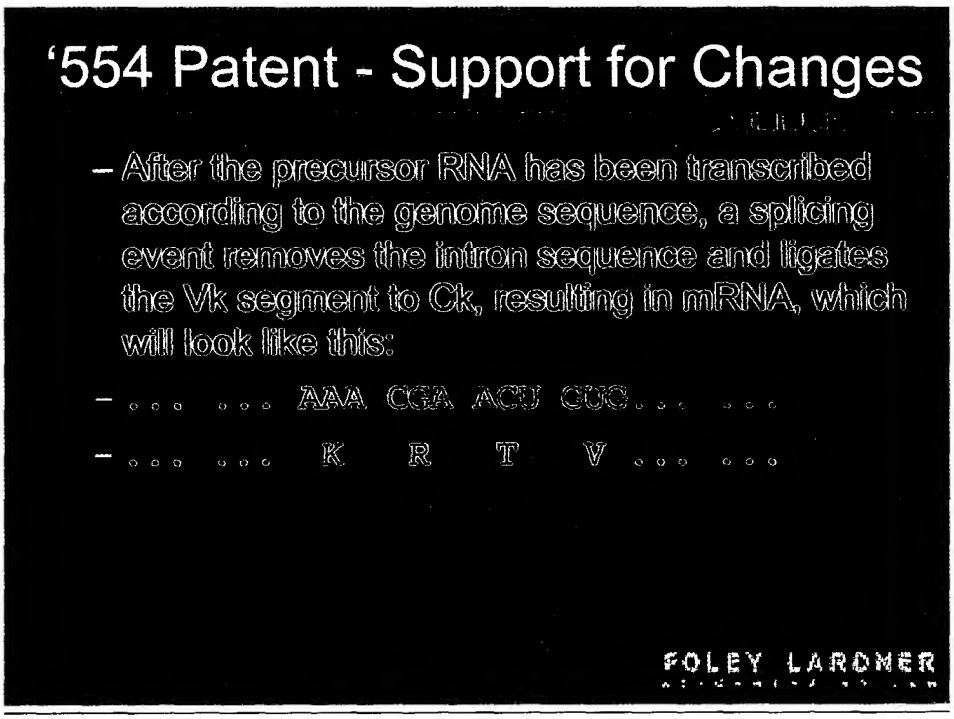
'554 Patent - Support for Changes
– After the precursor RNA has been transcribed according to the genome sequence, a splicing event removes the intron sequence and ligates the Vk segment to Ck, resulting in mRNA, which will look like this:
– ... ... AAA CGA ACU CUG ... ...
– ... ... K R T V ... ...
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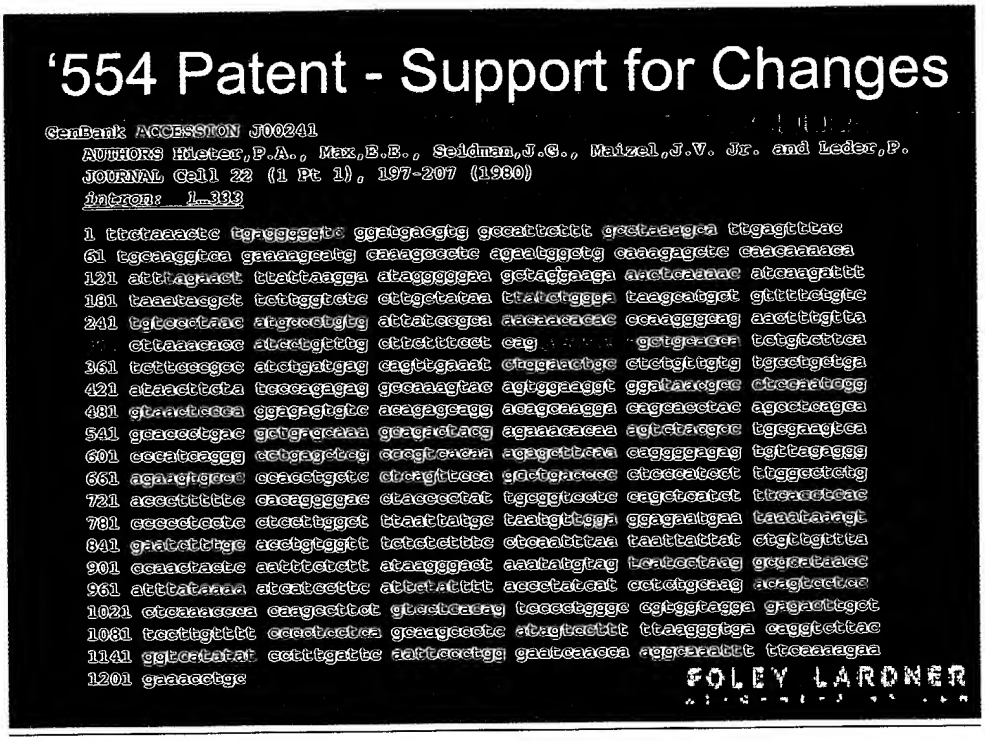
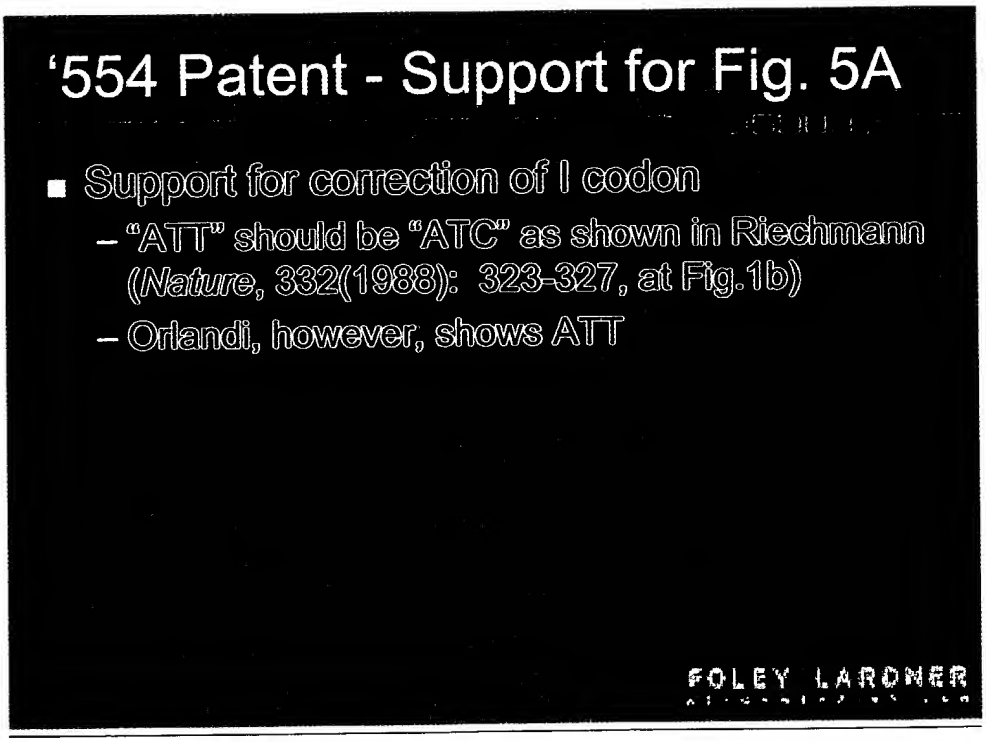


As noted by the explanation above, the sequence in FR4, "ICRSP" of the light chain variable region in Fig. 5A represents an intermediate product of the staging vector before insertion into the expression vector, pKH, as shown in Fig. 3A.



The scientific publications that are referred to above will be provided to the Examiner under separate cover.